Proceedings of ICEGEE 2026 Symposium: AI-Based Medicine and Biological Data Analysis
DOI: 10.54254/2753-8818/2026.AU31993

Folate Receptor α-Mediated Precision Therapy: A New Dimension in Individualized Treatment of Ovarian Cancer

Yingdan Liang

College of Pharmacy, Shenyang Pharmaceutical University, Shenyang, China
YingdanLiang@163.com

Abstract. Folate receptor alpha (FRα) has emerged as a pivotal biomarker and therapeutic target in epithelial ovarian cancer (EOC), a disease characterized by high mortality and limited treatment options upon platinum resistance. Its overexpression in a majority of EOCs, coupled with restricted expression in normal tissues, provides a compelling rationale for targeted intervention. This review synthesizes current evidence on the biological significance of FRα and the development of FRα-directed therapies, with a focus on antibody-drug conjugates (ADCs), particularly mirvetuximab soravtansine (MIRV). The accelerated approval of MIRV for FRα-high, platinum-resistant EOC (PROC) marks a paradigm shift, establishing the first biomarker-driven therapy in this setting. This paper examines the foundational preclinical and clinical trials that demonstrated the efficacy and manageable safety profile of MIRV, leading to its approval based on the SORAYA and confirmatory MIRASOL trials. The importance of accurate FRα assessment via companion diagnostics is highlighted, alongside discussions on mechanisms of action, mechanisms of resistance, and strategies to optimize patient selection and overcome therapeutic challenges. The integration of FRα-targeting agents into the ovarian cancer treatment landscape represents a significant advance in precision medicine, offering a new dimension of individualized care for patients with this challenging disease. Future directions include combination therapies and novel agent development to broaden the utility of FRα-targeting strategies. This study finds that mirvetuximab soravtansine significantly improves clinical outcomes, including overall survival, in patients with folate receptor alpha (FRα)-high, platinum-resistant ovarian cancer, thereby validating FRα as a robust therapeutic target.

Keywords: Folate receptor alpha (FRα), Ovarian cancer, Antibody-drug conjugate (ADC), Mirvetuximab soravtansine, Platinum-resistant ovarian cancer (PROC)

1. Introduction

Ovarian cancer continues to be the most deadly gynecologic malignancy, with an estimated five-year survival rate of approximately 50% [1]. Most patients have advanced-stage cancer when they first arrive, and although initial platinum-based chemotherapy is frequently successful, the majority will eventually relapse. Managing platinum-resistant ovarian cancer (PROC), which is characterized by disease recurrence within six months of finishing platinum-based therapy and has a poor prognosis with a median overall survival of 12–14 months and response rates to subsequent non-platinum

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.AU31993

chemotherapies usually below 15%, is a crucial challenge [2]. This harsh clinical reality emphasizes how urgently new, efficient, and well-tolerated therapeutic approaches are needed. The pursuit of targeted therapies has been a central focus in oncology, aiming to exploit specific molecular alterations unique to cancer cells while sparing healthy tissues. In ovarian cancer, folate receptor alpha (FRα) has been identified as a highly promising target. This glycosylphosphatidylinositol-anchored cell-surface glycoprotein mediates high-affinity folate uptake through receptor-mediated endocytosis [3,4]. Whereas FRα is normally confined to the apical faces of a few specialized epithelia, like kidney, choroid plexus and lung, it becomes dramatically up-regulated in 70–90 % of epithelial ovarian cancers, most strikingly in the high-grade serous subtype. This tumor-selective overexpression, often associated with more aggressive disease and worse outcomes, positions FRα as an ideal candidate for targeted therapy [5,6]. The development of FRα-targeted agents has evolved significantly. Early clinical investigations with farletuzumab, a monoclonal antibody targeting folate receptor alpha (FRα), demonstrated limited efficacy as a single agent—an outcome likely attributable to the absence of rigorous patient stratification based on FRα expression levels. The therapeutic paradigm shifted dramatically with the advent of antibody–drug conjugates (ADCs), which seamlessly integrate the exceptional specificity of monoclonal antibodies with the potent cytotoxicity of chemotherapeutic payloads. Mirvetuximab soravtansine (MIRV), the first-in-class ADC directed against FRα, consists of a humanized anti-FRα antibody covalently linked to DM4, a maytansinoid microtubule inhibitor that enables targeted delivery of lethal chemotherapy to tumor cells. Upon binding to FRα, MIRV is internalized, and the linker is cleaved within lysosomes, releasing the DM4 payload to induce cell cycle arrest and apoptosis. A key feature of MIRV is its "bystander effect," whereby the released payload can diffuse into and kill adjacent FRα-negative tumor cells, potentially overcoming tumor heterogeneity. The U. S. FDA's accelerated approval of mirvetuximab soravtansine in November 2022, for adults with FRα-positive, platinum-resistant epithelial ovarian cancer following one to three prior systemic therapies, represented a landmark milestone as the first targeted therapy and first antibody–drug conjugate approved for this challenging patient population [2]. This regulatory decision was underpinned by pivotal efficacy data from the single-arm SORAYA trial, which demonstrated an objective response rate of 31.7% and a median duration of response of 6.9 months in heavily pretreated patients [1]. These results were validated by the phase III MIRASOL study later, a randomized comparison that documented significant gains in both progression-free and overall survival for MIRV versus investigator-selected chemotherapy, securing its conversion to full regulatory approval.

This paper reviews the journey of FRα from a biological curiosity to a validated therapeutic target in ovarian cancer. It delves into the biology of FRα, the development and mechanism of action of FRα-targeting agents, particularly MIRV, and the critical clinical trial data that established its role in clinical practice. Furthermore, it discusses the essential role of companion diagnostics for patient selection, manages common toxicities, explores mechanisms of resistance, and outlines future directions, including combination strategies and novel agents. It promises to further refine and expand the application of FRα-mediated precision therapy.

2. The biology of folate receptor alpha (FRα) and its role in ovarian cancer

FRα, encoded by the FOLR1gene, is one of four isoforms of folate receptors (FRβ, FRα, FRγ, FRδ) with distinct expression patterns. Its architecture is characterized by a deep, open folate-binding pocket stabilized by disulfide bridges, enabling high-affinity folate engagement. In normal physiology, FRα is mainly expressed on the apical surface of polarized epithelial cells in specific tissues, including the proximal renal tubules, choroid plexus, and type I and II pneumocytes in the

DOI: 10.54254/2753-8818/2026.AU31993

lungs. This polarized expression limits its exposure to the systemic circulation, a feature that contributes to the favorable therapeutic index of FRα-targeting agents. In contrast, ovarian cancer cells exhibit a loss of polarity and high levels of FRα expression on the entire cell surface, making it readily accessible to targeted therapies. The precise mechanisms driving FRα overexpression in cancer are not fully elucidated but are thought to involve both genetic and epigenetic alterations. Gene amplification of the FOLR1locus on chromosome 11q13.3 has been observed in a subset of ovarian cancers and correlates with increased mRNA and protein expression [6]. Functionally, beyond its role in folate uptake to support one-carbon metabolism and nucleotide synthesis essential for rapid cell proliferation, emerging evidence suggests FRα may have roles in signaling transduction and even as a transcription factor, potentially contributing directly to oncogenesis. Studies have indicated that FRα can interact with key signaling pathways, including STAT3 and ERK, promoting cellular proliferation and survival. The expression of FRα is not uniform across all ovarian cancer histologies. It is most frequently and highly expressed in high-grade serous ovarian carcinoma (HGSOC), the most prevalent and aggressive subtype, with reports of overexpression in 60-85% of cases [3,5]. Other subtypes, such as clear cell and mucinous carcinomas, tend to have lower expression rates. Importantly, FRα expression is generally maintained during disease progression and after chemotherapy, making it a stable target in the recurrent setting [5]. Another critical aspect of folate biology in cancer is the role of other transporters, notably the Reduced Folate Carrier (RFC). RFC is a bidirectional, low-affinity, high-capacity transporter ubiquitously expressed in both normal and malignant tissues. It's interesting to note that a contradictory relationship has been found in ovarian cancer, where low RFC expression is frequently linked to high FRα expression, which is linked to a poor prognosis, and vice versa. High RFC expression has been correlated with better patient survival, suggesting it may act as a tumor suppressor or a favorable prognostic marker, potentially counterbalancing the oncogenic effects of FRα .

3. The development of mirvetuximab soravtansine (MIRV)

The concept of targeting FRα with an ADC is based on leveraging the receptor's efficient internalization capability. MIRV is engineered with three key components: the antibody (M9346A), a humanized IgG1 that binds FRα with high affinity and specificity; the linker sulfo-SPDB, a cleavable disulfide bridge that stays intact in the bloodstream but is rapidly severed within the reductive lysosomal milieu; and the payload (DM4), a potent maytansinoid derivative that prevents microtubule assembly, thereby inducing cell cycle arrest and apoptosis [2,7].

The mechanism of action involves a series of steps. After MIRV initially attaches itself to FRα on the surface of the tumor cell, the complex is taken up by endocytosis and transported to lysosomes. Within the acidic environment of the lysosome, the sulfo-SPDB linker is cleaved, releasing the DM4 payload. The free DM4 disrupts microtubule dynamics, ultimately triggering apoptotic cell death. A significant advantage of MIRV is the bystander effect; the hydrophobic DM4 metabolites can diffuse across cell membranes to kill neighboring FRα-negative cancer cells within a heterogeneous tumor, potentially overcoming a key mechanism of resistance [4,7]. The safety profile and initial activity of MIRV were established by early-phase trials (e.g., NCT01609556), which indicated a phase II dose of 6 mg kg^{-1} (adjusted ideal body weight) via intravenous infusion every three weeks. Adverse events were predominantly low-grade ocular toxicities accompanied by fatigue and gastrointestinal symptoms. All were readily managed with prophylactic steroid eye drops and timely dose modifications.

DOI: 10.54254/2753-8818/2026.AU31993

4. Pivotal clinical trials: SORAYA and MIRASOL

The single-arm phase II SORAYA trial (NCT04296890) provided the pivotal evidence that underpinned MIRV's accelerated approval. Enrolling 106 patients with FRα-high (≥75 % of cells showing ≥2+ intensity by VENTANA FOLR1 RxDx) platinum-resistant epithelial ovarian cancer who had received 1–3 prior regimens, such as mandatory bevacizumab, the study delivered practice-changing results: an investigator-assessed confirmed objective response rate of 31.7 % (5 complete and 29 partial responses) and a median duration of response of 6.9 months. Updated analyses revealed a median overall survival of 15.0 months, materially exceeding the ~12-month historical benchmark for this population [1]. Toxicity remained consistent with earlier experience; ocular events dominated but were mitigated by surveillance and protocol-directed interventions. These were definitively validated by the phase III MIRASOL trial (NCT04209855), a global, randomized study that allocated 453 FRα-high PROC patients 1:1 to MIRV or single-agent chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan). Gains from MIRV were both statistically and clinically significant: median progression-free survival 5.62 vs. 3.98 months, median overall survival (HR 0.65, $p<0.001$) 16.46 vs. 12.75 months (HR 0.67, $p=0.005$) and objective response rate 42.3% vs. 15.9% ($p<0.001$)—the first OS benefit seen in a phase III PROC trial, making MIRV the new gold standard for treatment. With reduced incidence of grade ≥3 adverse events (41.7% vs. 54.1%) and major adverse events, safety also favored the ADC [2].

5. Patient selection: the critical role of biomarker testing and companion diagnostics

MIRV's antitumor activity is tightly coupled to FRα density, so rigorous, reproducible biomarker testing is indispensable. The VENTANA FOLR1 (FOLR1-2.1) RxDx immunohistochemistry assay, approved in lock-step with the drug, identifies eligible patients as those with ≥75 % of viable tumor cells showing ≥2+ staining intensity. This "PS2+" threshold was refined after the phase III FORWARD I trial, which applied a looser criterion (≥50 % of cells at 1+ under 10× magnification), failed to meet its primary endpoint—underscoring the need to enrich for truly high expressors [4]. Adoption of the stricter PS2+ definition in SORAYA and MIRASOL successfully selected the population that derives clear benefit. Archival tissue reliably recapitulates FRα status, with high concordance to fresh biopsies, and inter-observer agreement among pathologists is substantial to almost perfect, supporting routine clinical robustness [8]. Accurate FRα scoring is therefore the linchpin for maximizing MIRV's therapeutic index.

6. Managing toxicity and future directions

The safety profile of MIRV is characterized by a distinct set of adverse effects that are generally manageable with proactive measures. Ocular toxicities, such as keratopathy (corneal changes) and visual disturbances, are the most common and are highlighted in a Boxed Warning in the prescribing information . These are thought to be off-target effects related to the DM4 payload, as FRα is not expressed in ocular tissues. Management strategies are critical and include mandatory baseline ophthalmic examination, prophylactic use of topical steroid eye drops and lubricating artificial tears throughout treatment, and prompt ophthalmic evaluation for any new or worsening ocular symptoms. Dose delays, reductions, or discontinuation may be necessary based on severity . Other notable toxicities include fatigue, gastrointestinal events (nausea, diarrhea), and peripheral neuropathy, which require supportive care and dose modifications. Future research is focused on expanding the utility of FRα-targeted therapies. Key directions include:

DOI: 10.54254/2753-8818/2026.AU31993

Preclinical and early clinical data suggest synergy between MIRV and other agents. Combinations with bevacizumab (anti-VEGF), PARP inhibitors (e.g., in homologous recombination deficient tumors or BRCA-mutated), and immunotherapies are under active investigation. The addition of mirvetuximab soravtansine to bevacizumab as a first-line maintenance therapy for patients with FRα-high, platinum-sensitive ovarian cancer is being tested in the pivotal phase III GLORIOSA study (NCT05445778).

Beyond ADCs, the pipeline is rapidly widening. Bispecific T-cell engagers (BiTEs) that reroute cytotoxic T lymphocytes toward FRα-expressing tumor cells, second-generation CAR-T products, and next-generation ADCs armed with topoisomerase I inhibitors, exemplified by MORAb-202, AZD5335, and STRO-002, are all advancing through pre-clinical and early clinical evaluation [9].

It's also critical to comprehend and overcome both primary and learned resistance to MIRV. Potential mechanisms include heterogeneous or loss of FRα expression, impaired internalization, and alterations in the microtubule apparatus. Strategies to address this include developing agents with enhanced bystander effects, combining therapies with non-overlapping resistance mechanisms, and exploring novel payloads.

Finally, there is a lot of interest in testing MIRV in platinum-sensitive recurrent and even first-line settings, maybe in conjunction with conventional chemotherapies, due to its effectiveness in PROC.

7. Conclusion

The approval and validation of mirvetuximab soravtansine represent a transformative advancement in platinum-resistant ovarian cancer management. It embodies the principles of precision medicine by leveraging a specific molecular target, FRα, to deliver effective therapy to a selected patient population. The compelling efficacy data from the MIRASOL trial, including a statistically significant overall survival benefit, have firmly established MIRV as a new standard of care for patients with FRα-high PROC. The journey of FRα from a biological marker to a validated therapeutic target underscores the importance of persistent scientific inquiry and robust clinical trial design. The success of MIRV has not only provided a much-needed effective option for a patient population with limited choices but has also reinvigorated the field of ovarian cancer therapeutics. It serves as a blueprint for the development of other targeted agents and highlights the indispensable role of companion diagnostics. As research continues to explore combinations, novel agents, and strategies to overcome resistance, the paradigm of FRα-mediated precision therapy is poised to expand, offering hope for further improvements in outcomes for women with ovarian cancer.

As a review, this study is limited by its lack of original experimental data, which constrains mechanistic depth, and a potentially non-exhaustive literature scope. Future work should integrate functional experiments and broader literature surveys to validate and refine the role of FRα in ovarian cancer precision therapy.

References

[1] Coleman, R. L., Lorusso, D., Oaknin, A., Cecere, S. C., Denys, H., Colombo, N., van Gorp, T., Konner, J. A., Romeo Marin, M., Harter, P., Murphy, C., Wang, Y., Esteves, B., Method, M., & Matulonis, U. A. (2024). Mirvetuximab soravtansine in folate receptor alpha (FRα)-high platinum-resistant ovarian cancer: Final overall survival and post hoc sequence of therapy subgroup results from the SORAYA trial. International Journal of Gynecological Cancer, 34(8), 1119–1125. https: //doi.org/10.1136/ijgc-2024-005401

[2] Dilawari, A., Shah, M., Ison, G., Gittleman, H., Fiero, M. H., Shah, A., Hamed, S. S., Qiu, J., Yu, J., Manheng, W., Ricks, T. K., Pragani, R., Arudchandran, A., Patel, P., Zaman, S., Roy, A., Kalavar, S., Ghosh, S., Pierce, W. F., …

DOI: 10.54254/2753-8818/2026.AU31993

Amiri-Kordestani, L. (2023). FDA approval summary: Mirvetuximab soravtansine-gynx for FRα-positive, platinum-resistant ovarian cancer. Clinical CancerResearch, 29(19), 3835–3840.https: //doi.org/10.1158/1078-0432.CCR-23-0991

[3] Zannoni, G. F., Angelico, G., d'Amati, A., D'Alessandris, N., Scaglione, G., Urtueta, B. P., Ferrara, G., Caliò, A., Campisi, P., De Leo, A., Guerini Rocco, E., Iuzzolino, M., Lerda, L., Paolini, B., Punzi, A., Vinci, M., Troncone, G., & Santoro, A. (2025). Interobserver agreement in immunohistochemical evaluation of folate receptor alpha (FRα) in ovarian cancer: A multicentre study. International Journal of Molecular Sciences, 26(16), 7687. https: //doi.org/10.3390/ijms26167687

[4] Liu, Y., Chen, X., Evan, T., Esapaa, B., Chenoweth, A., Cheung, A., & Karagiannis, S. N. (2025). Folate receptor alpha for cancer therapy: An antibody and antibody-drug conjugate target coming of age. mAbs, 17(1), 2470309. https: //doi.org/10.1080/19420862.2025.2470309

[5] Previs, R. A., Strickland, K. C., Wallen, Z., Ko, H., Green, M., Cooper, M., Lyon, E., Biorn, M., Armetta, J., Quarles, R., Watson, C. H., Ring, K., Klein, J. L., Caveney, B., Severson, E. A., & Ramkissoon, S. (2025). Analysis of real world FRα testing in ovarian, fallopian tube, and primary peritoneal cancers. Gynecologic Oncology, 192, 102–110.

[6] Siu, M. K. Y., Kong, D. S. H., Chan, H. Y., Wong, E. S. Y., Ip, P. P. C., Jiang, L., Ngan, H. Y. S., Le, X.-F., & Cheung, A. N. Y. (2012). Paradoxical impact of two folate receptors, FRα and RFC, in ovarian cancer: Effect on cell proliferation, invasion and clinical outcome. PLOS ONE, 7(11), e47201. https: //doi.org/10.1371/journal.pone.0047201

[7] Gunderson, C. C., & Moore, K. N. (2016). Mirvetuximab soravtansine. FRα-targeting ADC; treatment of epithelial ovarian cancer. Drugs of the Future, 41(9), 539–545. https: //doi.org/10.1358/dof.2016.041.09.2544475

[8] Martin, L. P., Konner, J. A., Moore, K. N., Seward, S. M., Hess, S. M., Abrams, S. I., Kozbor, D., Odunsi, K., & Zsiros, E. (2017). Characterization of folate receptor alpha (FRα) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: A phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine. Gynecologic Oncology, 147(2), 402–407. https: //doi.org/10.1016/j.ygyno.2017.08.015

[9] McGray, A. J. R., Chiello, J. L., Tsuji, T., Long, M., Maraszek, K., Gaulin, N., Rosario, S. R., Hess, S. M., Abrams, S. I., Kozbor, D., Odunsi, K., & Zsiros, E. (2023). BiTE secretion by adoptively transferred stem-like T cells improves FRα+ ovarian cancer control. Journal for ImmunoTherapy of Cancer, 11(8), e006863. https: //doi.org/10.1136/jitc-2023-006863